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Neurotoxic effects associated with antibiotic use: management considerations

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The clinical manifestations of antibiotic-induced neurotoxic effects, the underlying mechanisms and management strategies have been reviewed. PubMed and OVID searches (January 1960–June 2010) were conducted using search terms such as antibiotics, side effects, neurotoxicity and encephalopathy which yielded approximately 300 articles. All relevant case reports, case series, letters and retrospective reviews describing neurotoxic effects and those discussing mechanisms of neurotoxicity were included.
Antibiotic-induced neurotoxic side effects can have a myriad of neurologic presentations. Patients with prior central nervous system (CNS) disease, renal insufficiency and advanced age may be particularly vulnerable. Treatment consists of discontinuation of the offending agent, use of antiepileptic drugs in the case of seizures or status epilepticus and haemodialysis in certain cases. The risk of CNS toxicity may be reduced via dosage adjustments in high risk populations. Awareness of the potential neurotoxic clinical manifestations of various antibiotics and high degree of vigilance in critically ill patients is essential in identifying a potentially serious, though reversible complications of antibiotic therapy particularly with the advent of newer antimicrobial agents.

Introduction

Antibiotics are among the most frequently used pharmaceuticals in both the inpatient and outpatient setting. While these antimicrobial agents are generally well tolerated, these drugs are not without their associated side effects, both dose-dependent and idiosyncratic in nature. While diarrhoea is a commonly associated adverse effect of many antibiotics, toxic effects on the central nervous system are perhaps much less recognized [1]. A danger for clinicians and patients alike, of not recognizing neurotoxic effects of antibiotics is that the neurological manifestations of toxicity may be confused with a different neurological condition. Correspondingly, in cases of drug-induced encephalopathy, change in mental status may be ascribed to a metabolic abnormality especially in hospitalized patients. With greater education regarding these neurotoxic effects, medical care providers can learn to recognize toxic effects more readily and make medication adjustments as necessary since it is often a readily reversible process. A high degree of suspicion is also essential for clinicians.

Many factors of drug metabolism may increase susceptibility to neurotoxicity such as an individual's nutritional status, local blood flow and tissue uptake, and status of the blood-brain barrier, rate of absorption of the medication, route of drug delivery to target tissue, activation and elimination of the drug and its metabolites, as well as protective responses the individual may have [2]. Other factors that may be implicated include genetic factors, altered drug pharmacokinetics in cases of renal insufficiency and central nervous system (CNS) penetration may also be relevant in causing neurotoxicity [3]. In this article, we reviewed the neurologic adverse effects of different classes of antibiotics as they have been described in the medical literature over the last several decades, the potential mechanisms and management strategies.

Methods

We conducted a Medline/OVID search to include publications that were reported after 1960 relating to antibiotic neurotoxicity using search terms: antibiotics, toxicity, neurotoxicity, encephalopathy and seizures. The initial search yielded approximately 300 articles. All relevant case reports, case series, letters to editor, prospective and retrospective reviews, addressing the salient features of the neurotoxicity of different groups of antibiotics were included. The majority of those included were case reports, letters to editor or case series which offer low levels of

evidence. Moreover, articles addressing mechanisms of neurotoxicity and evaluation strategies in cases of neurotoxicity was also extracted. The papers included upon review and agreement of both authors. The neurotoxic clinical features of specific antibiotic in each group was extracted from the included papers, were then discussed. Strategies for management of antibiotic neurotoxicity was also extracted from all the papers and reviewed.

Results

Aminoglycosides

Aminoglycosides have been known to cause ototoxicity most commonly, though peripheral neuropathy, encephalopathy and neuromuscular blockade have also been reported (Table 1). In the case of gentamicin, one case series outlined peripheral neuropathy and encephalopathy, with nerve biopsy revealing a lysosomal abnormality analogous to those changes seen in gentamicin-induced nephrotoxicity [4]. Other case studies have detailed brain lesions following administration of intrathecal gentamicin, where the patient developed multiple small discrete lesions restricted to the pons and mesencephalon characterized by axonal loss, astrocytic and oligodendroglial loss as well as an inflammatory response. A concurrent experimental study in rabbits resulted in reproduction of similar characteristic lesions that were directly related to brain tissue and CSF concentrations of gentamicin [5].

Aminoglycoside antibiotics are also associated with neuromuscular blockade. Since the original observations were made with streptomycin in patients with tuberculosis, many other aminoglycoside antibiotics have been implicated in neuromuscular and autonomic transmission blockade [5]. They include amikacin [6], tobramycin [7], neomycin [8], gentamicin [9], and kanamicin [9]. These neuromuscular blocking effects of aminoglycosides have implications in neurological conditions such as myasthe-

Table 1

Neurotoxicity associated with aminoglycosides and all beta-lactams, their mechanisms of neurotoxicity and risk factors

Antibiotic class	Number of publications	Neurotoxic effects	Mechanism of neurotoxicity	Risk factors
Aminoglycosides: **1. Gentamicin** **2. Streptomycin** **3. Amikacin** **4. Tobramycin** **5. Neomicin** **6. Kanamycin**	5: retrospective case reviews; case series; case reports	Ototoxicity-class effect Peripheral neuropathy; encephalopathy (gentamicin) Neuromuscular blockade-class effect	Activation of NMDA receptors Lysosomal abnormality; Axonal loss; Inflammatory response Inhibition of pre-synaptic quantal release of acetylcholine and binding of drug to postsynaptic receptors	Increased CNS permeability Intrathecal administration
Beta lactams- **Cephalosporins:** ***High risk agents*:** **1. Cefazolin** **2. Cefesolis** **3. Ceftazidime** **4. Cefoperazone** **5. Cefepime** ***Low risk agents*:** **1. Cephalexin** **2. Cefatoxime** **3. Ceftriaxone**	24- Case reports; retrospective reviews; review articles	Encephalopathy with Triphasic waves on EEG Tardive seizures Seizures NCSE Myoclonus Asterexis	Inhibition of GABA-A release; Increased glutamate; Induction of endotoxins; Cytokine release	Renal failure Prior CNS disease Older age Excess dosage
Beta-lactams- **Penicillins:** **1. Benzylpenicillin** **2. Peniclin G** **3. Pipercillin** **4. Ticarillin** **5. Ampicillim** **6. Amoxacillin** **7. Oxacillin**	4: Case reports; case series	Seizures Tardive seizures Encephalopa Tremors	Inhibition of GABA-A receptors	Renal failure; low birth weight-neonates
Beta-lactams **Carbapenems** **1. Imepenem** **2. Meropenem** **3. Paripenem** **4. Ertapenem** **5. Doripenem** **6. Ceftaroline**	4: Case reports	Encephalopathy Seizures Myoclonus Headache	Inhibition of GABA-A receptors; Possibly binding of glutamate	Renal failure

nia gravis or Lambert Eaton myasthenic syndrome, where these antibiotics can worsen neuromuscular weakness and thus are contraindicated in these patients.

The mechanism of ototoxicity is thought to be the result of excitotoxic activation of NMDA receptors within the cochlea [10]. This results in formation of oxidative radicals, which are postulated to contribute to cell death [11]. Intrastriatal neomycin is shown to cause gliosis that was dose-dependent and diminished when NMDA antagonists were co-administered. It stands that there is a theoretical dose-dependent risk of CNS toxicity with aminoglycosides, particularly in individuals with increased CNS permeability [10]. The mechanism of neuromuscular blockade on the other hand appears to be inhibition of quantal release of acetylcholine in the neuromuscular junction presynaptically, and also binding of the drug to the acetylcholine receptor complex post-junctionally [12]. Calcium seems to prevent this suggesting calcium depletion may occur as well [12].

Cephalosporins

Neurotoxicity has been reported with first generation cephalosporins such as cefazolin, second generation such as cefuroxime, third generation such as ceftazidime and fourth generation such as cefepime and can range from encephalopathy to non-convulsive status epilepticus [13] (Table 1). This is particularly true in the setting of renal impairment though cases also exist in those with normal creatinine clearance. Previous CNS disease has also been suggested as decreasing the threshold of nervous system toxicity with use of third and fourth generation cephalosporins [14]. In addition to pre-existing CNS conditions, reduced creatinine clearance, impaired renal function and excess dosage of medication have been described as independent risk factors for neurotoxic effects [15]. The typical time period for encephalopathy induced by cephalosporin use is a latency of 1 to 10 days following start of medication, and resolution in 2 to 7 days following discontinuation [16].

Clinical presentations of cephalosporin-associated neurotoxicity include tardive seizures, encephalopathy, myoclonus, truncal-asterixis, seizures, non-convulsive status epilepticus (NCSE) and coma [13]. One case series described eight patients who developed neurotoxicity with use of cephalosporins in the setting of renal failure. Their myriad of neurological symptoms included lethargy, confusion, agitation, global aphasia, chorea-athetosis, seizures, myoclonus and coma, which were slowly progressive in evolution. EEGs of all patients demonstrated diffuse slowing with triphasic waves suggestive of toxic-metabolic encephalopathy (without any epileptiform features) [17]. Mortality was high in all cases.

Cephalosporins such as cefuroxime, cefixime and cefazolin have also been associated with a reversible encephalopathy with temporo-spatial disorientation and triphasic waves on EEG [18–25]. Those with compromised renal function are thought to be at higher risk for the encephalopathy [26–28]. NCSE has been frequently reported with the fourth generation cephalosporin, cefepime. Given that the seizures are subclinical, the only clinical feature may be a non-localizing encephalopathy, and ultimately EEG is required to make this diagnosis. Patients often require anticonvulsants such as benzodiazepines, phenytoin and valproic acid for treatment of NCSE, albeit temporarily [13]. Cefepime has also been implicated in increased risk of unexplained mortality in hospitalized neutropenic patients when compared with treatment with other antibiotics [29]. Therefore care providers should implement a high degree of surveillance when using cefepime among neutropenic or renally compromised patients.

Pathogenesis of neurotoxicity in renally impaired patients appears to be mediated by rise in serum concentrations, increased permeability of the blood-brain barrier secondary to blood urea increase, carbamylation, glycation or other chemical protein modification, as well as build up of toxic organic acids within the cerebrospinal fluid [30]. Increased circulating unbound antibiotic also contributes to the vulnerability of renally compromised patients to CNS toxicity [31, 32]. As with other beta-lactams, the basic mechanism for this neurotoxicity includes decreased gamma-aminobutyric acid (GABA) release from nerve terminals, increased excitatory amino acid release, as well as cytokine release [33, 34]. Other postulated mechanisms for cephalosporin neurotoxicity also include induction of endotoxins and, possibly, glutaminergic mechanisms. Laboratory studies also show that cephalosporins with high affinity for GABA-A receptors and those with high penetrance through the blood-brain barrier are more neurotoxic [34].

Penicillins

Penicillins are known to cause a wide spectrum of neurotoxic manifestations including encephalopathy, behavioural changes, myoclonus, seizures as well as NCSE (Table 1). A history of CNS disease has been described as a risk factor for encephalopathy associated with beta-lactam use [13]. Piperacillin has been implicated in cases of tardive seizures. In one report, two patients treated with piperacillin for pneumonia during a course of electro-convulsive therapy (ECT) for schizophrenia, developed recurrent seizures over a 2 day period approximately 8 days after the third ECT session. Each of these lasted 15 to 40 s and occurred intermittently 5 to 15 times daily. Interictal EEG was without any focal abnormality [35].

Though reportedly less neurotoxic in comparison with benzylpenicillin, piperacillin has been implicated in an encephalopathy characterized by dysarthria, tremor, behavioural changes, progressive confusion, and finally several generalized tonic-clonic seizures in patients with end-stage renal disease [36, 37]. Seizures continued despite anticonvulsant medications and encephalopathy resolved only after high-flux haemodialysis was used. This phenomenon has also been described as PIPE (piperacillin-

induced encephalopathy) and has previously been confused with primary CNS infection or infarction.

Ampicillin-induced neurotoxicity has also been described in the literature in very low birth weight neonates. This particular population is thought to be at risk for neurotoxic effects secondary to elevated drug serum concentrations which translate to elevated CSF concentrations (due to immature transport mechanisms and renal immaturity), as well as increased permeability of the blood-brain barrier (possibly due to meningeal inflammation, immaturity of the cerebrovascular system or underlying CNS disease) [38]. Detecting seizures in infants remains problematic as more than 50% of neonates are estimated to have seizures without any obvious clinical manifestations, and when they do are often subtle. This particular example underscores the importance of recognizing which antibiotics are associated with neurotoxicity as its presence may not be evident clinically.

More than either oxacillin or ampicillin, benzylpenicillin appeared to have the most epileptogenic potential, independent of CSF concentrations of the antibiotic [39]. Flucloxacillin was shown to induce irritable patterns on EEG such as bursts of spikes and polyspikes [40].

Penicillins are believed to exert an inhibitory effect on GABA transmission due to their beta-lactam ring structure, which shares similar structural features to those of GABA neurotransmitters [41]. This is further supported by studies in which the beta-lactam ring is enzymatically cleaved and the epileptogenic potential is subsequently lost [42]. Thiazolidine ring and side chain length may have an impact on the epileptogenic potential [42]. In addition, it has been demonstrated in rat studies that penicillin can quantitatively reduce benzodiazepine receptors and thus reduced inhibition and altered neuronal excitability [43].

Other beta-lactams: carbapenems

Carbapenems are reported to be associated with seizures with an estimated incidence of 3% [13] (Table 1). Risk factors associated with this neurotoxicity again are advanced age, history of CNS disease, renal insufficiency, as well as low body weight. There are several reports neurotoxic effects consisting of encephalopathy both in patients with end-stage renal disease or mild renal dysfunction several days following intravenous administration of imipenem [44–46]. Serum concentrations of imipenem were elevated in some cases suggesting that toxicity is from reduced clearance in the setting of renal insufficiency [46]. In addition, carbapenems are also associated with seizures, mostly generalized tonic-clonic seizures, though simple and complex partial seizures have also been reported [47]. The neurotoxic potential of carbapenems also had serious potential implications in the treatment of bacterial meningitis. In fact, in a trial of imepenem-cilastin for bacterial meningitis in children (age 3–48 months), seven out of 25 developed seizures acutely which resulted in the trial being stopped prematurely [48]. High CSF penetration of the drug is cited as the likely cause of high rate of seizures in the study.

The newer beta-lactam antibiotics include doripenem, ceftobiprole and ceftaroline. Post-marketing studies suggest that doripenem may be associated with the potential for epileptogenicity seen with other carbepenems. However animal models did not develop seizures when administered doripenem both intravenously and intracisternally [49, 50]. A common adverse effect of both doripenem and ceftaroline is headache [51]. While no case reports were found describing CNS toxicities with use of these antimicrobials, these are yet to be widely used and therefore the potential for neurotoxicity is unknown at this time.

As with other antibiotics with a similar chemical structure, this seizure provocation of carbepenems is likely related to inhibition of GABA-A receptors, and possibly binding to gluatamate [52]. A difference in the variable propensity to induce convulsions between ertapenem and meropenem when compared with imipenem/cilastatin may be related to their variations in chemical structure. Doripenem, appears to have less neurotoxic effects as shown by *in vitro* studies showing reduced affinity to GABA-A receptors compared with meropenem, imipenem and panipenem [53]. N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazolepropionate receptor complex interactions have also been suggested as an alternative mechanism of epileptogenicity [54]. Furthermore, the more basic the side chain of the carbapenem molecule, the more epileptogenic potential there is, due to increased affinity to the GABA-A receptor. The C2 side chain of meropenem is much less basic than those of imipenem and panipenem, and so it follows that the former is less associated with neurotoxic effects than the latter [53].

Tetracyclines

Tetracyclines have been associated with cranial nerve toxicity and neuromuscular blockage [55]. In addition, some cases of benign intracranial hypertension have been attributed to a tetracycline-induced neurotoxic event [56] (Table 2).

Trimethoprim/sulfonamides

Trimethoprim/sulfamethaxazole (TMP-SMX) has been reported to be associated with encephalopathy and psychosis (Table 2). A case of transient psychosis secondary to trimethoprim-sulfamethoxazole administration was reported, where the patient developed an acute delirium with agitation, visual and auditory hallucinations. Once the offending medication was discontinued, psychosis/delirium slowly resolved [57]. In elderly or immunocompromised patients, cases of encephalopathy and aseptic meningitis have been described [58, 59]. Patterson *et al*. [60] also described a case of transient tremors occurring in an immuno-competent patient taking TMP-SMX. While the neurotoxic effects are thought to be at least in

Table 2

Neurotoxicity associated with all other groups of antibiotics, mechanisms and risk factors

Antibiotic class	Number of publications	Neurotoxic effects	Mechanism of neurotoxicity	Risk factors
Tetracyclines	1: Review article	Cranial nerve toxicity; Neuromuscular blockade; Intracranial hypotension		
Trimethoprim-Sulfametaxazole	8: case reports	Transient psychosis; encephalopathy; aseptic meningitis	CNS penetration	Advancing age; Immunocompromized
Macrolides.azalides: **1. Erythromycin** **2. Clarithromycin** **3. Azithromycin,** **4. Dirithromycin**	6: Case reports; Review articles	Ototoxicity	Damage to Cochlea	
Quinolones: **1. Ciprofloxacin** **2. Norfloxacin** **3. Ofloxacin** **4. Gemifloxacin** **5. Levofloxacin** **6. Gatifloxacin**	5: Case reports; case series	Psychosis Encephalopathy Seizures NCSE Orofacial dyskinesias Action myoclonus Ataxia Dysarthria Chorea	Inhibition of GABA-A receptors; Activation of NMDA receptors	Advancing age; Impaired renal function; Increased permeability of blood-brain barrier
Oxazolidinones **1. Linezolid**	4: case reports; case series	Encephalopathy Bells palsy Optic neuropathy	Not known	
Streptogramins: **1. Dalforpistin-quinupristin**	1: case report	Headache		
Polymixins **1. Polymyxin B** **2. Colistin**	5: case reports; case series; retrospective reviews	Chemical Arachnoiditis Seizures Diplopia Ataxia Paresthsias Polyneuropathy Myasthenia-like syndrome	High affinity binding to CNS Blocking acetylcholine receptors; Prolonged depolarization via calcium depletion	Co-administration of narcotics, anaesthetics, muscle relaxants; Myasthenia gravis Renal failure Cystic fibrosis
Others: **1. Clindamycin** **2. Vancomycin** **3. Nitrofurantoin** **4. Chloramphenicol** **5. Metronidazole**	10: case reports; case series	Tardive dyskinesia; Extrapyramidal syndrome Ventriculitis Polyneuropathy, benign intracranial hypotension Optic neuritis Ataxia Dysphagia Peripheral neuropathy	CSF inflammatory response Cerebellar/brain stem lesions Axonal damage	Impaired renal function

part related to the excellent CNS penetration of TMP-SMX, the exact mechanism of neurotoxicity is unknown [59].

Macrolides/azalides

Macrolides are extensively used in the treatment of upper respiratory infections and have been linked to ototoxicity via damage to the cochlea. This may result in equilibrium dysfunction in addition to hearing impairment. Early detection (which may be quite challenging for critically ill patients) is essential in order to minimize future risk of permanent damage to the vestibulocochlear system [61].

Quinolones

Neurotoxic manifestations associated with quinolones include seizures, confusion/encephalopathy, myoclonus and toxic psychosis (Table 2). Complex partial status epilepticus or NCSE documented by EEG have been reported with ciprofloxacin-induced neurotoxicity in patients presenting with altered mental status or confusion [62]. One case report described generalized myoclonus with delirium with ciprofloxacin [63]. That being said, EEG manifestation of fluoroquinolone-associated delirium, range from normal EEGs to diffuse slowing [64, 65]. Interestingly, CNS penetration of fluoroquinolones does not always correlate with the potential for epileptogenicity [66]. In contrast to ciprofloxacin, ofloxacin has an increased CNS permeability of 50% of the serum concentration, though interestingly less cases of neurotoxicity have been reported for ofloxacin than for ciprofloxacin [67].

New quinolone derivatives or gyrase inhibitors include levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin,

gatifloxacin and moxifloxacin and are the most commonly implicated drugs causing neurotoxic side effects among quinolones. These were first described with use of ofloxacin [68]. Levofloxacin is the active levo-stereoisomer of oflaxacin, and a third-generation fluorinated quinolone, which is reported to cause pronounced acute delirium associated with psychotic features [65, 69] as well as seizures [70]. Similar acute psychotic reactions were also reported with ofloxacin [71]. In post-marketing reports CNS toxic effects of gyrase inhibitors have an incidence of 0.89%, with primarily symptoms listed as headache, insomnia, dizziness and restlessness and, less commonly, delusions and hallucinations [72].

Oro-facial dyskinesias have also been reported with quinolones. The drugs implicated include ciprofloxacin and ofloxacin, in the absence of a metabolic abnormality and at extremes of age [73, 74]. Ofloxacin may be associated with neurotoxicity via improved CNS barrier penetration. In one case, a 71-year-old male presented with spitting, profuse sweating and insomnia, in addition to echolalia, echopraxia, orofacial and limb automatisms, and hypersalivation. This Tourette-like syndrome begs a possible interaction of antibiotic with the central dopaminergic system [75]. Quinolone treatment also resulted in extrapyramidal manifestations such as gait disturbance, dysarthria and choreiform movements [76]. Gemifloxacin, another quinolone, is associated with neurotoxicity, which manifests as an encephalopathy. Pharmacodynamics are significant in implicating this neurotoxic effect as plasma gemifloxacin concentration peaks following one dose [77]. In one large analysis of 6775 patients, CNS reactions occurred in approximately 2.8% of patients given gemifloxacin, with 1.2% complaining of headache and 0.8% with dizziness [78].

Postulated mechanisms for fluoroquinolone-mediated CNS toxicity include inhibition of GABA-A receptors as well as activation of excitatory NMDA receptors [79]. Using quantitative EEG, rat studies with norfloxacin showed dose-dependent neurotoxic effects, i.e. increased epileptic discharges and behaviours were seen in those groups who were exposed to higher doses. This can be further extrapolated to the clinical situation in which the blood-brain barrier may already be compromised, therein placing the patient at even increased risk of elevated drug concentrations and potential neurotoxic effects [80]. As postulated for fluoroquinolone-induced seizures, disruption of the GABAergic system is implicated in the development of fluoroquinolone-induced orofacial dyskinesias [81]. Variability in binding potency of quinolones to the GABA-A receptors may explain the variability in neurotoxic effects [82].

Oxazolidinones

These broad-spectrum antibiotics are traditionally reserved for treatment of vancomycin-resistent enterococcal (VRE) infections (Table 2). There has been at least one case report of probable linezolid-related encephalopathy as well as a case report of Bell's palsy coinciding with linezolid treatment for osteomyelitis which occurred a second time with rechallenge of the implicated antibiotic for recurrent infection [83]. In addition, a persistent, painful peripheral neuropathy has also been associated with use of this antibiotic, particularly with extended use and with concomitant use of selective serotonin re-uptake inhibitors (SSRIs) [84]. Optic neuropathy has also been associated with use of linezolid [85].

Streptogramins

This medication is also typically reserved for use in the treatment of VRE infections. Adverse effects associated with this antibiotic are limited to headache, arthralgias and myalgias [86].

Polymyxins

Polymyxins at one time actually fell into disuse secondary to concerns of neuron and nephrotoxicity, but with the emergence of multi-drug resistant gram-negative bacilli, these drugs have renewed relevance, particularly in the treatment of nosocomial infections [87]. Neurologic side effects have been reported with an incidence as high as 7% to 27%. These typically consist of paresthesias and ataxia, and less commonly, diplopia, ptosis and nystagmus [88, 89] (Table 2). With use of both polymyxin B and colistin, cases of chemical arachnoiditis following intrathecal or intraventricular administration have been reported [90, 91]. This may be associated with clinic signs of menigismus and seizures [92]. At low doses, it appears that sulfate forms of polymyxins, i.e. polymyxin B, are more toxic, while the unsulfated forms, i.e. colistin, are less toxic. This variation in toxicity between the two chemically different forms is not seen at higher doses/concentrations of these agents [92].

More recent studies have shown paresthesias and polyneuropathy that can occur in up to 7% of patients using polymyxin B [93–98]. It is also noteworthy that since recent use of poylmyxins has been reserved for critically ill patients who may already be ventilation-dependent, some of the milder neurologic effects previously reported such as paresthesias, may go undetected [89]. Paresthesias are more common with intravenous use (seen in 27% of patients) compared with intramuscular use (7.3% of patients) of polymyxin [99, 100]. A more serious side effect described is that of ventilation-dependent respiratory failure/apnoea following intramuscular injections of polymyxin, lasting 10 to 48 h. This is believed to be a myasthenia-like syndrome [100], though there are no further reports in the last two decades [101, 102]. Other neurological side effects reported include visual disturbances, vertigo, confusion, hallucinations, ataxia, seizures and partial deafness.

Proposed mechanisms for polymyxin induced neuromuscular blockade include presynaptic blockade of the

release of acetycholine [103, 104]. The other possibility is a prolonged depolarization phase secondary to calcium depletion [105]. Despite the similarity of polymixin's toxicity to myasthenia gravis, studies using cholinesterase inhibitors to treat neuromuscular blockade have been conflicting/inconclusive [103, 106]. Polymyxin associated neurotoxicity is thought to be dose-dependent as it directly correlates with the concentration of active metabolite within the blood. In rat studies, for example, rates of neurotoxicity increased with extended dosing of colistemethate [107]. Some of the increased incidence of CNS effects has been related to high binding of polymyxins to brain tissue [108] and interaction with neurons on the basis of their high lipid content [97]. Risk factors associated with the development of neurotoxic effects include administration of polymyxins with narcotics, sedatives, anaesthetic drugs, corticosteroids, and/or muscle relaxants [109]. Patients with a history of myasthenia gravis or with renal impairment are also at increased risk of developing respiratory insufficiency/neuromuscular blockade [110]. Interestingly, while nephrotoxic effects are equivalent in both genders, the neurotoxic effects are seen more commonly in women [106].

Metronidazole

Metronidazole can have cerebellar toxicity that manifests clinically with varying degrees of limb and gait ataxia and dysarthria (Table 2). Symptoms are accompanied by characteristic T2 high signal lesions on brain MRI in the cerebellum and brainstem. Neurotoxicity was seen after prolonged use of metronidazole with clinical symptoms resolving within 3–7 days of discontinuation of the medication, while follow-up MRIs also show resolution of cerebellar lesions [111]. While the precise mechanism for neurotoxicity is not entirely clear, one hypothesis is that it occurs via axonal swelling secondary to metronidazole-induced vasogenic oedema [112]. Peripheral neuropathy is another recognized potentially neurotoxic effect with use of metronidazole. One report describes a 53-year-old who developed encephalopathy, dysarthria, ataxia and a length-dependent peripheral neuropathy in the context of prolonged metronidazole therapy (a cumulative dose of 146 g over 88 days). Multiple skin biopsies confirmed evidence of a small fibre sensory neuropathy [113]. In another case reporting the rapid development of peripheral neuropathy related to metronidazole with electrophysiologic studies demonstrating prolonged distal motor latencies, mildly decreased compound muscle action potential and decreased sensory nerve action potentials involving the posterior tibial and peroneal nerves to varying degrees were noted [114]. Optic neuropathy, as well as autonomic neuropathy, have also been described in association with metronidazole use [115, 116]. Other neurological adverse effects ascribed to metronidazole include dizziness, headache and confusion [117].

Other antibiotics

Clindamycin is not known to have major neurotoxic effects, though one case report described a child who developed abnormal movements characterized by 'hiccough-like or twitch-like' abdominal movements that then spread to involve abnormal movements of shoulder and jaw which resolved after discontinuation of clindamycin [118].

Vancomycin has been implicated in local neurotoxic effects when used in the treatment of ventriculitis. Nava-Ocampo *et al*. [119] described the case of a neonate who developed ventriculitis along with CSF pleocytosis and eosinophilia after intraventricular administration of vancomycin for *Enterococcus fecalis*. This effect was thought to be mediated by vancomycin-induced inflammatory process within the CSF. A dose adjustment to 5 mg day^{-1} of vancomycin is recommended when administered intraventricularly [120].

Nitrofurantoin when used in children is associated with a sensorimotor polyneuropathy, typically manifesting as dysaesthesias and paresthesias beginning in the distal lower extremities [121, 122]. Fifteen cases have been reported in the literature in children, the majority of whom had some component of renal dysfunction [123]. The incidence of polyneuropathy has been estimated to be at 0.0007% [124]. There was also a case of a 10-month-old with benign intracranial hypertension believed to be secondary to nitrofurantoin reported in the 1970s [125]. All of these neurologic adverse effects resolved following discontinuation of the implicated medication.

Chloramphenicol is considered a broad spectrum antibiotic and has been implicated in a case of bilateral optic neuritis [126, 127].

Management strategies

Identification of risk factors associated with neurotoxicity is imperative and perhaps the most important initial step. As previously mentioned, these include extremes of age, impaired renal function, history of central nervous system disease, and/or damage to the blood-brain barrier (Figure 1). Other important factors to consider are body size (volume of distribution), as well as co-administration with other medications with neurotoxic and/or nephrotoxic effects, as well as any epileptogenic potential [41]. Apart from altered mental status induced by the antibiotic itself, the nephrotoxicity sometimes induced by antibiotics may itself be responsible for the encephalopathy. Early diagnosis is therefore essential in minimizing neurotoxic adverse effects. Thus avoidance of neurotoxic agents in patients with the above-mentioned risk factors is critical in preventing neurotoxicity.

Proper diagnosis may be obscured by the overall clinical picture as changes in mental status may easily be attributed to the infectious process that is mandating the use of antibiotic treatment, or to an underlying metabolic

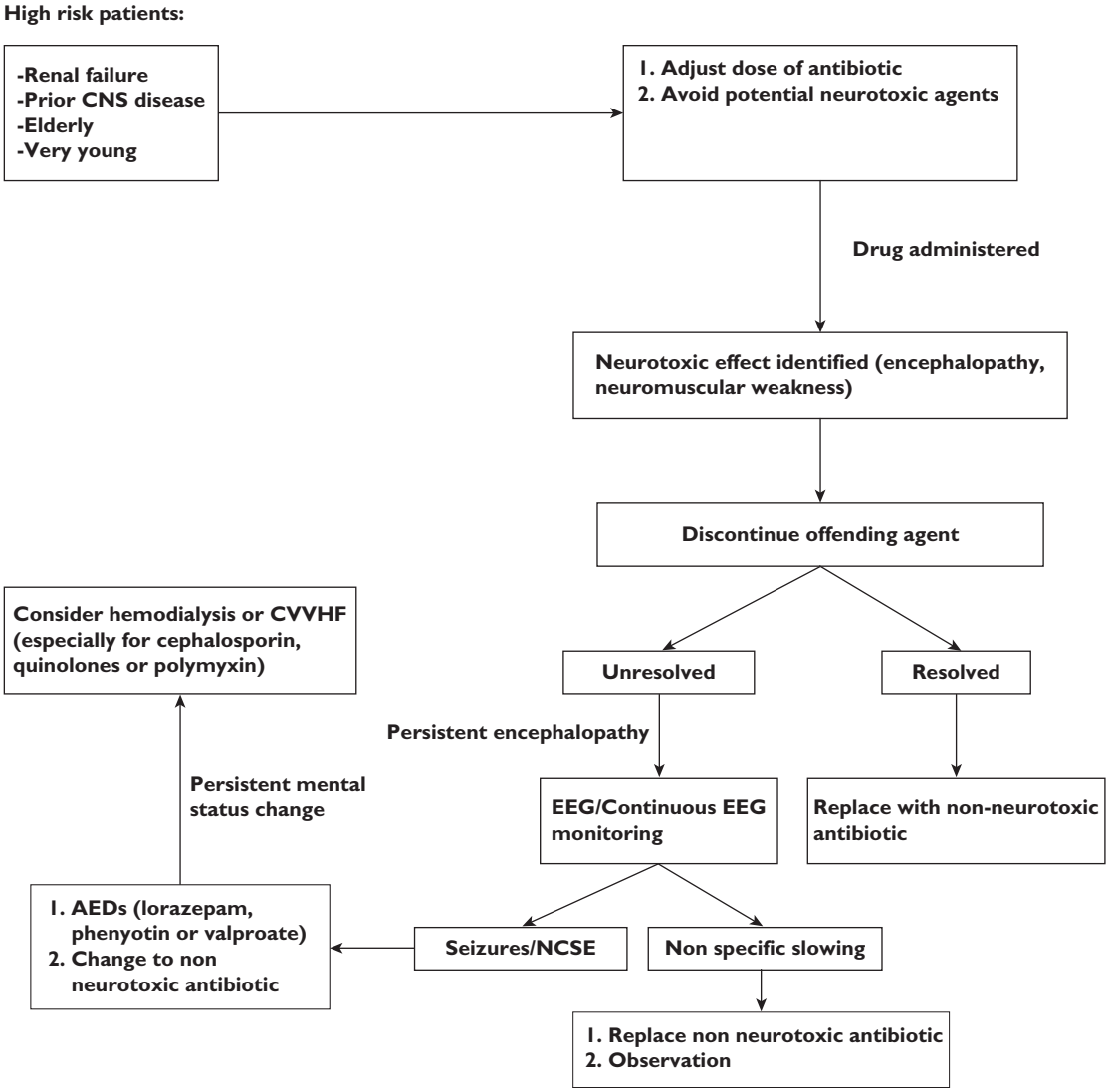

Figure 1
Management algorithm for antibiotic neurotoxicity: high risk patients

disorder such as renal failure [26]. Emergent EEG may be useful, since drug-induced NCSE may be readily detected. As NCSE may potentially be lethal, emergent EEG or EEG monitoring should be considered by clinicians in any patient who develops encephalopathy after administration of potentially neurotoxic antibiotics. Furthermore, EEG can be helpful in distinguishing drug induced NCSE *vs.* drug-induced encephalopathy. Once identified, the offending agent should be discontinued immediately and replaced with a non-neurotoxic agent. In cases of seizures or NCSE, anticonvulsants may be needed, albeit temporarily. In cases of polymyxin induced myasthenic syndrome, ventilatory support may be needed depending on the degree of respiratory impairment [110].

In cases with impaired renal function, once it is established that neurotoxicity is caused by the antibiotic, haemodialysis or haemofiltration may be required for adequate clearance of the drug. This may be in the form of high-volume continuous venovenous haemofiltration (CVVHF) to optimize drug clearance [128]. As a drug, cefepime is amenable to CVVHF secondary to its low affinity for protein binding [129]. This also underscores the need to adjust judiciously medication doses in the setting of impaired drug metabolism, i.e. renal dysfunction.

It may not necessarily be practical to avoid administration of all of the aforementioned antibiotics associated with neurotoxicity. However, knowledge about which agents are commonly implicated and what manifestations are frequently seen may translate to more pro-active care. Furthermore, identification of those populations at increased risk of these neurotoxicities will allow for better care of the patient. Hospital-based intensive monitoring

has been shown to be an effective way of detecting relationships between drug exposure and consequent adverse drug reactions [130]. Diligent vigilance is necessary to identify potential neurotoxic effects so as to treat patients and educate other health practitioners effectively.

Conclusions

Neurotoxicity is common among many groups of antibiotics in at-risk patients and can range from ototoxicity, neuropathy and neuromuscular blockade to confusion, nonspecific encephalopathy, seizures and status epilepticus. Populations at risk of neurotoxicity associated with various groups of antibiotics include those with extremes of age, critical illness, renal dysfunction and prior neurological disease. Knowledge of neurotoxic effects is essential for clinicians in order to avoid this preventable complication. Clinicians should recognize that CNS toxicity may be underestimated and among those with encephalopathy, EEG should be considered in order to diagnose NCSE. Knowledge of selection of an appropriate antibiotic, pharmacokinetics and dosage adjustments in those at risk may aid in the prevention of neurotoxicity associated with these drugs.

Competing Interests

There are no competing interests to declare.

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